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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,968	11/06/2001	Carlos Miguel Carcagno	1909.0040002	7301

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EXAMINER

KAUSHAL, SUMESH

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/830,968

Applicant(s)

CARCAGNO ET AL.

Examiner

Sumesh Kaushal Ph.D.

Art Unit

1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 06 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 11601.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 03/03/04 has been acknowledged.

Claims 1-12 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306.

Priority

1. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Argentina on 11/06/1998 (980105611) and 02/23/1999 (990100681). It is noted, however, that applicant has not filed a certified copy of the 980105611 and 990100681 application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 1-3 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Jixian et al (Bull Acad. Mil. Med. Sci. 21(4):244-246, 1997, English translation provided).

The instant claims are drawn to a method for obtaining human erythropoietin by culturing mammalian cells, which express recombinant human erythropoietin in a culture medium comprising insulin. The instant claims are further drawn to mammalian cells selected from the group comprising CHO, COS, BHK, Namalwa, and HeLa. The claims are further drawn to the method wherein the culture medium comprises fetal calf-free media.

Jixian et al teaches production of recombinant human erythropoietin (rHuEPO) using CHO cells in a serum free media (SFM-p) in the presence of insulin (see abstract). Regarding claim 1-3 specifically the cited art teaches genetically engineered mammalian cells (CHO cells), which express recombinant human erythropoietin (page 2, para. 1.1). Regarding claim 6 the cited art teaches culturing of rHuEPO producing cells in a fetal calf serum-free media designated as SFM-p (page 2; page 4, para. 2.1; page 5 para. 2.2, table-3). The cited art further teaches that the SFM-p comprises various additives, which include Se, Ethanolamine, vitamins, peptone, insulin, transferin and some cytokines added in DMEM and F12 medium (abstract, page 2, para. 1.2). In addition the cited art teaches that SFM-p promotes growth and proliferation of rHuEPO expressing CHO cells, which resulted in the production of rHuEPO in culture media. Thus the cited art clearly anticipate the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. Claims 4-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jixian et al (Bull Acad. Mil. Med. Sci. 21(4):244-246, 1997) as applied to claims 1-3 and 6 above, and further in view of Koch et al (EP 0513738 A2, 11/19/1992, *English translation provided*).

Claims 4-5 are drawn to method for obtaining human erythropoietin by culturing mammalian cells, which express recombinant human erythropoietin in a culture medium

comprising insulin, wherein the culture media comprises insulin in the range of 1-20 mg of insulin per liter of culture media.

Jixian et al teaches production of recombinant human erythropoietin (rHuEPO) using CHO cells in a serum free media (SFM-p) in the presence of insulin (see abstract). Regarding claim 1-3 specifically the cited art teaches genetically engineered mammalian cells (CHO cells), which express recombinant human erythropoietin (page 2, para. 1.1). Regarding claim 6 the cited art teaches culturing of rHuEPO producing cells in a fetal calf serum-free media designated as SFM-p (page 2; page 4, para. 2.1; page 5 para. 2.2, table-3). The cited art further teaches that the SFM-p comprises various additives which include Se, Ethanolamine, vitamins, peptone, insulin, transferin and some cytokines added in DMEM and F12 medium (abstract, page 2, para. 1.2). In addition the cited art teaches that SFM-p promotes growth and proliferation of rHuEPO expressing CHO cells, which resulted in the production of rHuEPO in culture media.

Even though Jixian teaches production of recombinant human erythropoietin (rHuEPO) using CHO cells in a serum free media (SFM-p) in the presence of insulin, the reference does not specifically teaches that insulin concentration is in the range of 1-20 mg of insulin per liter of culture media.

Koch et al teaches a serum-free culture medium containing insulin for the cultivation of mammalian cells, especially the genetically engineered CHO cells to produce recombinant erythropoietin¹ (page 1). Regarding claims 4-5, the cited art teaches that the serum-free media contains recombinant insulin in the range of 0.1-20 mg/L (page 2 para. 4-6, page 3 para. 2). The cited art further teaches serum free media that comprises recombinant insulin at the concentration of 5mg/L, which is well with in the range of insulin concentration as claimed (i.e 1-20mg/L) see page 4 para. 7, table-1; page 6). The cited art further teaches production of erythropoietin in the culture medium by cultivating genetically engineered CHO (encoding EPO), in a serum free culture media containing insulin (page 3, para.3; page4 para.3; page 6).

¹ Even though Koch et al teaches a serum-free culture medium containing insulin for the cultivation of genetically engineered CHO cells to produce recombinant erythropoietin, Koch et al does not specifically teach that the recombinant erythropoietin produced is of human origin.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the teaching of Jixian by incorporating the SFM-p with insulin in the range of 1-20mg/L in view of Koch. One would have been motivated to do so because incorporation of insulin in the range of 1-20mg/L in serum free media is close to cultivation conditions when serum is used. One would have a reasonable expectation of success to produce rHuEPO in CHO using serum free media containing insulin in the range of 1-20mg/L because the cited prior clearly teaches that CHO cells proliferate and produce recombinant EPO under such conditions (see Koch fig-1). Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

4. Claims 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jixian et al (Bull Acad. Mil. Med. Sci. 21(4):244-246, 1997 as applied to claims 1-3 and 6 above, and further in view of Yanagi et al (DNA 8(6):419-427, 1989) and Chiba et al (US 3865801, 1975).

Claims 7-10 are drawn to a method for separating supernatant from cells, concentrating the supernatant approximately 50-150 folds and freezing concentrated product. In addition the instant claims are drawn to a method wherein media is added to cells from which the supernatant is separated and culturing the media fed cells.

Jixian et al teaches production of recombinant human erythropoietin (rHuEPO) using CHO cells in a serum free media (SFM-p) in the presence of insulin (see abstract). Regarding claim 1-3 specifically the cited art teaches genetically engineered mammalian cells (CHO cells), which express recombinant human erythropoietin (page 2, para. 1.1). Regarding claim 6 the cited art teaches culturing of rHuEPO producing cells in a fetal calf serum-free media designated as SFM-p (page 2; page 4, para. 2.1; page 5 para. 2.2, table-3). The cited art further teaches that the SFM-p comprises various additives, which include Se, Ethanolamine, vitamins, peptone, insulin, transferin and some cytokines added in DMEM and F12 medium (abstract, page 2, para. 1.2). In addition the cited art teaches that SFM-p promotes growth and proliferation of rHuEPO expressing CHO cells, which resulted in the production of rHuEPO in culture media.

Regarding claim 7 (b) and 8 Jixian further teaches batch separation of culture media obtained from EPO producing CHO cells (page 5 table-3).

However, Jixian does not specifically teach the concentration of supernatant obtained from genetically engineered CHO cells containing EPO (approximately 50-150 fold). In addition Jixian does not teach freezing the concentrated product.

Yanagi et al teaches isolation of recombinant human erythropoietin produced by Namalwa cells (abstract). Regarding claim 7(c) and 9-10 the cited art teaches separation of EPO containing supernatant from EPO-producing 2A311 cells. The cited art further teaches concentration of EPO from the cell supernatant. The cited art teaches concentration of 2A311 media from 4 liters to 400 ml using an ultra filtration device. The cited art teaches further concentration of media obtained by ultra filtration using CM Affi-gel Blue column and a hydroxylapatite column. The purified preparation was then further concentrated by ultra-filtration followed by gel-permeation on TSK G3000SW columns (page 420, col.2 para. 4, page 422 table-1). The cited art teaches that such a purification procedures resulted in a purification factor that ranges from 17-5390 folds (page 422, table-1).

Chiba et al teaches a method of storing EPO for prolonged periods of time. Regarding claim 7 (d), the cited art teaches storing purified EPO preparation in the frozen state at -20°C (col. 7, lines 4-12).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Jixian by employing purification strategy to concentrate EPO containing media as taught by Yanagi. One would have been motivated to do so because highly purified preparation of EPO is desirable product for clinical uses. In addition it would have be further obvious to store the purified EPO preparation in a frozen state in view of Chiba, since cyropreserved proteins have increases stability. One would have a reasonable expectation of success in doing so, since purification of recombinant proteins from the host cells and cyropreservation of purified protein was routine in the art at the time of filing. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

5. Claims 7 and 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jixian et al (Bull Acad. Mil. Med. Sci. 21(4):244-246, 1997 as applied to claims 1-3 and 6 above, and Yanagi et al (DNA 8(6):419-427, 1989) and Chiba et al (US 3865801, 1975) as applied to claims 7-10 above and in further in view van Reis et al (US 5490937, 1996).

The instant claims are drawn to the method for obtaining human erythropoietin from a mammalian cell culture by concentrating the separated supernatant containing EPO using tangential filtration system through membranes with a molecular cut-off of about 3,000 Daltons. The claims are further drawn to a method sterile filtering the concentrated product through membranes with pores of dia meter of about 0.2 mm.

Jixian et al teaches production of recombinant human erythropoietin (rHuEPO) using CHO cells in a serum free media (SFM-p) in the presence of insulin (see abstract). Regarding claim 1-3 specifically the cited art teaches genetically engineered mammalian cells (CHO cells), which express recombinant human erythropoietin (page 2, para. 1.1). Regarding claim 6 the cited art teaches culturing of rHuEPO producing cells in a fetal calf serum-free media designated as SFM-p (page 2; page 4, para. 2.1; page 5 para. 2.2, table-3). The cited art further teaches that the SFM-p comprises various additives, which include Se, Ethanolamine, vitamins, peptone, insulin, transferin and some cytokines added in DMEM and F12 medium (abstract, page 2, para. 1.2). In addition the cited art teaches that SFM-p promotes growth and proliferation of rHuEPO expressing CHO cells, which resulted in the production of rHuEPO in culture media. Regarding claim 7 (b) and 8 Jixian further teaches batch separation of culture media obtained from EPO producing CHO cells (page 5 table-3).

Yanagi et al teaches isolation of recombinant human erythropoietin produced by Namalwa cells (abstract). Regarding claim 7(c) and 9-10 the cited art teaches separation of EPO containing supernatant from EPO-producing 2A311 cells. The cited art further teaches concentration of EPO form the cell supernatant. The cited art teaches concentration of 2A311 media from 4 liters to 400 ml using an ultra filtration device. The cited art teaches further concentration of media obtained by ultra filtration using CM Affi-gel Blue column and a hydroxylapatite column. The purified preparation

was then further concentrated by ultra-filtration followed by gel-permeation on TSK G3000SW columns (page 420, col.2 para. 4, page 422 table-1). The cited art teaches that such a purification procedures resulted in a purification factor that ranges from 17-5390 folds (page 422, table-1).

Chiba et al teaches a method of storing EPO for prolonged periods of time. Regarding claim 7 (d), the cited art teaches storing purified EPO preparation in the frozen state at -20°C (col. 7, lines 4-12).

However, Jixian, Yanagi and Chiba do not teach purification of EPO from culture media via a tangential filtration system and sterile filtration of concentrated product.

van Reis et al teaches a tangential flow filtration process and apparatus for separating species of interest (proteins) from a mixture. Regarding claim 11 the cited art teaches a tangential filtration system through filtration membranes having a pore size that separate species of interest having molecular weight of about 1 to 1000 kDa. The cited art further teaches that ultra filtration membranes for tangential-flow filtration are available as units of different configuration depending upon the volume of the liquid to be handled and variety of pore sizes. Regarding claim 12, the cited art further teaches filtration through micro porous membranes that has a pore size typically from 0.1 to 10 micrometers, which would inherently sterile the filtered product (col.12 lines 12-34). The cited art further teaches that use of tangential flow filtration system for higher fold purification of species of interest (col.4 lines 47-61).

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Jixian, Yanagi and Chiba by employing a purification strategy that involves a tangential filtration system and sterile filtration in view of van Reis. One would have been motivated to use tangential filtration system to accomplish large-scale resolution macromolecular mixtures obtained from cell culture media. One would have a reasonable expectation of success, since isolation of protein via tangential flow filtration process was routine in the protein purification art at the time of filing. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sumesh Kaushal
Examiner Art Unit 1636


SUMESH KAUSHAL
PATENT EXAMINER